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Effect of recombinant interferon ∝ 2 on clinical course of first episode genital herpes infection and subsequent recurrences

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SUMMARY Herpes genitalis is an infection associated with considerable morbidity. Acyclovir, though effective, must be taken daily to prevent recurrences. The effects of interferon on this infection were therefore investigated. In a randomised double blind study, 31 patients with first episodes of genital herpes infection were studied to assess the effect of interferon on the presenting episode and on recurrences. Interferon (5×10^6 IU) was administered once daily subcutaneously during a five day "treatment" period followed by a three month "maintenance" period (1×10^6 IU three times weekly). Interferon had no effect on first episode herpetic attacks. During interferon administration women showed a trend towards reduced healing time and viral shedding in recurrences, but the differences were not significant and no effect was noted in women after administration of interferon. Interferon reduced assessed healing time and viral shedding in recurrences, however, in men ($p=0{\cdot}05$) during interferon administration, and this continued as a trend after treatment.

Introduction

Until recently, no effective treatment was available for genital herpes simplex virus (HSV) infections. Acyclovir (acycloguanosine) ointment has been effective in first episodes of herpes, particularly in women,[1 2] and has accelerated healing in men with recurrent herpes,[3] and acyclovir tablets have been effective in treating first episode genital herpes[4] and recurrent herpes,[5 6] and supressing recurrent disease successfully if taken daily.[7 8] The drug is not curative, and the high cost of treatment as well as the unknown toxicity of long term administration[9] make it a less than satisfactory solution to the problem.

Recombinant interferon α 2 can be produced in virtually limitless quantities, and at "low" doses it has minimal side effects such as fever, chills, and muscle aches, which occur in most patients for one to three days of the treatment period. This study was therefore undertaken to assess the effect of parenterally administered interferon α 2 on the clinical course of first episodes of genital herpes infection, and on recurrences occurring in the same patients.

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Patients and methods

STUDY POPULATION

We studied patients referred to the infectious diseases clinic at this hospital with first episodes of genital herpes of less than five days' duration who had no history of vesicular or ulcerative genital lesions. Those with antibodies at a titre of less than 1/8 at time of entry were considered to have primary infection, whereas those with titres of 1/8 or more were thought to have initial infection. Patients included had no other clinically important disease, were aged 18 or older, and were men or women who were not pregnant and had been taking oral contraceptives or using intrauterine contraceptive devices for at least three months before the start of the study. Patients were excluded from the study if they: had appreciable secondary genitourinary infections; had any cardiac, hepatic, gastrointestinal, renal, or neurological disease or clotting abnormality; had been exposed to any investigational drug within one month before the start of the study; had been exposed to any other interferon preparations within one month before the start of the study; had received any other systemic antiviral treatment within 30 days before entry to the study; had received any topical antiviral agents within seven days of entry into the study; had any immunosuppressive disease or were receiving immunosuppressive treatment; required concomitant

prostaglandin synthetase inhibiting compounds; or yielded negative viral cultures for HSV at the time of enrolment. The study was conducted in accordance with the ethical standards of the Committee on Human Experimentation, and all patients gave signed informed consent.

We assessed all lesions, whether first episode or recurrence, and described them as macules, papules, pustules, vesicles, ulcers, crusted, or healed. The healing time of lesions was calculated as the time between entry and complete re-epithelialisation of all lesions. The duration of viral shedding was calculated as the time from entry until the first negative lesion culture. We recorded the date of onset of signs and symptoms, as well as their severity.

We treated patients with subcutaneous injections of 2 interferon 5×10^6 IU daily for five days (the treatment phase) immediately followed by 1×10^6 IU three times a week for 12 weeks (maintenance phase). Control patients received placebo injections according to the same schedule.

ASSESSMENT OF RECURRENT LESIONS

We evaluated recurrent lesions by HSV culture, staging, progress, location (sketched on a case record diagram), and laboratory studies. We assessed all recurrent lesions for healing time and viral shedding from the time of onset. We assessed for healing time both lesions that were culture positive for HSV and those observed but culture negative.

Virological and serological methods

Lesions were cultured by rolling a rayon swab over the bases of two lesions, and the swabs were vigorously agitated in 1 ml Hank's balanced salt solution viral transport medium. The supernatant was transferred into two tubes of W138 cell cultures containing medium 199 with 2% fetal bovine serum and penicillin 100 μ/ml, streptomycin 100 μg/ml, and amphotericin 1 μg/ml. The two inoculated tubes were observed for cytopathogenic effect on alternate days for 14 days.

We identified and typed isolates as HSV-1 or HSV-2 by indirect immunofluorescence with monoclonal antibodies using the "Herpes ID Kit" (Armand Frappier Institute, Laval, Quebec, Canada). We tested serum complement fixation antibodies to HSV-1 and HSV-2 when patients entered the study.

Material for HSV cultures was taken from the endocervix of all women patients and from the urethra of all men. Any extragenital lesions were also cultured.

FOLLOW UP FOR RECURRENCES

We followed up all patients during the maintenance phase and at monthly intervals after the end of the maintenance phase for a period of six months. Immediately a recurrence occurred, we examined and followed up the patient.

STATISTICAL ANALYSIS

We analysed data by Wilcoxon's non-parametric rank sum test for two independent samples.

Results

STUDY POPULATION

Thirty one patients (13 men, 18 women) were enrolled in the study from June 1983 to January 1984. Two women were excluded during the maintenance phase of the study because of non-compliance. The remaining 29 patients completed their entire course of interferon treatment.

Differentiation between the side effects of the interferon and the symptoms of the disease was not possible while the study was blind, but the differences became evident when the code was broken. Most of the symptoms listed below lasted for one to three days and in a few patients ended after the first week. Of the 14 patients treated with interferon, 12 had fever, 10 headache, 11 chills, seven myalgia, five nausea, three vomiting, eight fatigue, eight anorexia, and one diarrhoea. All had neutropenia during the treatment

TABLE 1 *Characteristics of 31 patients with first episode genital herpes simplex virus (HSV) infections treated with interferon or placebo*

	Patients treated with:					
	Interferon		*Placebo*		*Total*	
	Men	*Women*	*Men*	*Women*	*Men*	*Women*
No of patients	6	10	7	8	13	18
Mean age (years)	31	27	33	25		
No with primary disease*	3	4	0	7	3	11
No with initial disease†	3	6	7	1	10	7
No with type 1 HSV	1	5	3	5	4	10
No with type 2 HSV	5	5	4	3	9	8
Mean duration of lesions at entry (days)	2·3	3·0	3·3	2·9		
No developing recurrences during study period	3	7	4	5	7	12

* Primary disease = complement fixing antibody titres $< 1/8$.
† Initial disease = complement fixing antibody titres $\geq 1/8$.

period only (5×10^6 IU daily), and no patient was excluded from the study because of side effects.

Of the 15 patients receiving placebo, one had fever, three headache, two chills, three myalgia, two nausea, one vomiting, five fatigue, and one anorexia during the first one to four days.

Table I outlines the characteristics of all the patients. The two treatment groups were comparable in age, and the proportion of men and women in the two treatment groups was not significantly different.

Three patients had a history of oral herpes. Ten men and seven women had initial infections, as indicated by the titre of complement fixing antibody to HSV type 1 or 2 in serum taken at the acute phase. Primary and initial infections were distributed equally in the groups receiving interferon. In men receiving placebo all infections were initial, whereas in women receiving placebo seven out of eight infections were primary.

On initial presentation herpetic lesions at sites other than the penis or vulva were noted in the urethras of three men, the rectums of two men, the cervices of nine women, and the oral labia of one woman.

EFFECTS OF INTERFERON ON FIRST EPISODE INFECTIONS

Table II shows the duration of signs and symptoms in all 31 patients during the five day treatment phase. In neither men nor women did the daily administration of 5×10^6 IU of interferon ∝2 have any effect on the duration of pain or viral shedding, the percentage of patients forming new lesions, or the duration of new lesions. Interferon was well tolerated, and the only side effects noted in some patients were those outlined above. No other hematological or biochemical abnormalities were noted.

EFFECTS OF INTERFERON ON TIME TO FIRST RECURRENCE AND NUMBER OF RECURRENCES

In neither men nor women did the administration of interferon have an effect on the time to first recurrence or on the number of recurrences (see table III).

HEALING AND VIRAL SHEDDING TIME IN RECURRENCES IN MEN DURING AND AFTER INTERFERON ADMINISTRATION

Table III shows that interferon had no effect on the

TABLE II *Mean duration of signs and symptoms of disease in 31 patients at the time of presentation and during five day treatment period (numbers are days except where stated)*

	Men receiving:		*Women receiving:*	
	Interferon (n=6)	*Placebo (n=7)*	*Interferon (n=10)*	*Placebo (n=8)*
Mean duration* of pain	5·3	4·7	4·4	3·6
Mean duration* of itching	2·3	3·8	3·9	4·6
Mean duration* of dysuria	2·3	0·9	4·4	2·5
Mean duration* of inguinal adenopathy	1·8	2·4	2·0	1·6
Mean duration* of vaginal discharge			4·0	2·5
Mean duration† of viral shedding	6·1	8·6	5·2	6·6
Mean duration‡ of healing	10·0	13·5	9·6	7·8
No (%) of patients developing new lesions	3(50)	2(29)	2(20)	3(38)
Duration of new lesions	6·0	9·0	6·5	4·6

* Time from onset to presentation.
† Time from entry to first negative culture from lesions.
‡ Time from entry to healing of genital and extragenital lesions.

TABLE III *No of recurrences, mean healing time, and mean duration of viral shedding in 28 patients (12 men and 16 women)* during and after administration of interferon*

	During administration of:			*After administration of:*		
	Interferon	*Placebo*	*Difference*	*Interferon*	*Placebo*	*Difference*
Men						
No of patients	3	4		2	3	
Total No of recurrences†	8 (6)	9		5 (4)	9 (7)	
Mean healing time (days)	3·4	8·5	p=0·05	5·3	8·6	NS
Mean duration of viral shedding (days)	1·8	5·5	p=0.05	1·8	2·9	NS
Women						
No of patients	2	3		7	4	
Total No of recurrences†	11 (7)	5 (4)		11 (9)	5	
Mean healing time (days)	3·6	7·6	NS	8·2	5·5	NS
Mean duration of viral shedding (days)	1·0	3·7	NS	5·2	2·8	NS

* One man (with rectal infection only) and two women (who did not comply with treatment) excluded from analysis.
† Numbers include culture negative and positive lesions and were used to calculate healing time. (Numbers in parentheses are culture positive lesions only and were used to calculate duration of shedding.)

number of recurrences, but significantly shortened viral shedding time ($p=0{\cdot}05$) in men during its administration. Thus the nature of the recurrences was affected and, though there was a trend for this effect to continue after stopping interferon treatment, the trend was not significant. Two of the men who had recurrences during interferon treatment had primary infection and one had initial infection.

HEALING AND VIRAL SHEDDING TIME IN RECURRENCES IN WOMEN DURING AND AFTER INTERFERON ADMINISTRATION

Table III shows that, though there was a definite trend for duration of viral shedding and time to healing to be shorter during interferon administration in women, the differences were not significant. No effect was noted in women after administration of interferon was stopped.

Discussion

The results of this study clearly show that interferon α2 had no effect on first episode genital herpes infections in either men or women. Though it did not affect the number of recurrences, it did have a significant effect on their nature in men during the administration of interferon. The time to healing and duration of viral shedding were up to six months shorter in men after administration of the maintenance phase of interferon, though the reduction in duration of viral shedding was not significant. The number of patients was small, and further experiments are needed to confirm these results. There was a trend towards shortened viral shedding and healing times in women receiving interferon, but these results were not significant. No trend was noted in women after maintenance treatment with interferon was stopped. A sex difference in response to the treatment of genital herpes has been noted previously, as decreased healing time was seen only in men receiving acyclovir ointment in recurrent infections.[3]

An experimental model of genital herpes infection in guinea pigs (Kern, unpublished observation) using human recombinant interferon α A (Roche) showed that, if the interferon was administered for seven days beginning 24 hours after inoculation of the animals, the course of the initial episode was strikingly altered, and there was a decrease in the number of recurrences after the interferon was discontinued. If interferon was not administered until 72 hours after viral inoculation, however, the effect on the initial episode was less pronounced, and there was no effect on recurrences after the seven days of interferon treatment. These data suggest that interferon may act more as an immunomodulator than as an antiviral agent in this animal model, and that the way in which the initial episode is treated with interferon can affect the subsequent course of the disease, namely the recurrences.

Interferon was well tolerated at the doses used, but was administered for a long time (five days of treatment and three months of maintenance doses given three times weekly), which clearly is not a practical regimen. Furthermore, having to inject interferon makes it inconvenient to use for a long time. The dose and duration of interferon treatment were arbitrarily decided, however, and administration for a much shorter "treatment" time with occasional "booster" injections may be adequate. Additional trials with various dosage schedules are required to confirm this. Interestingly, other workers have shown that interferon α 2 has no effect on recurrent herpetic infections.[10] In that study, however, unlike the study published here, interferon was not given during the first episode of the infections. In the study reported here, interferon given during the first episode of infection possibly had an immunomodulating rather than antiviral action, which manifested itself by an effect on the recurrences. More needs to be learned about the biological activities of interferon before the above phenomenon can be understood.

The results of this study suggest a possible new approach to the treatment of genital herpes. In men there was a significant effect on recurrences during administration of interferon and a beneficial trend for six months after maintenance treatment. Recombinant interferon α 2 was used in this study but other interferons, such as ß or γ, may possibly be more effective in managing genital herpes infections.

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